REMARKS

Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections in view of the foregoing amendments and following remarks. Claims 43, 44, 45, and 46 are new. Claim 7 has been cancelled without prejudice to filing a divisional application directed thereto. Claims 20 and 39 have been cancelled and rewritten as claims 45 and 46, respectively. Claims 10, 12, 13, and 41 have been amended to place the claims in better condition for examination and to place the claims in conformance with standard U.S. practice.

Claims 20, 39, and 41 were objected to for depending on non-elected claims. These claims have been amended and made dependent on elected claims. Claim 20 has been rewritten as claim 45. Claim 39 has been rewritten as claim 46.

Claims 20, 39, and 41 were objected to for reciting a use without setting forth any steps involved in the process. Claims 20 (new claim 45) and 39 (new claim 46) have been amended to method claims, which include steps in the process. Claim 41 has been amended to a composition claim.

Claims 12 and 39 were rejected for having a broad range together with a narrow range. The narrow range, "colon cancer," has been deleted from claim 12

and presented in dependent claim 43. The narrow range, "SEQ. ID No: 7," has been deleted from claim 39 and submitted in dependent claim 44.

Claims 20, 39 and 41 were rejected for not setting forth any steps involved in the use of a nucleic acid. Claims 20 (new claim 45) and 39 (new claim 46) have been amended to include method steps. Claim 41 has been amended to a composition claim.

Claims 10-13 were rejected for missing essential steps. The Examiner saw a gap as to evidence that would link an increase in 7a5/prognostin as being indicative of colon carcinoma or predictive of any tumor disease. In response, applicants refer to figure 4 of the application and the last paragraph of page 19 of the specification. The last paragraph of page 19 states that Prognostin expression is elevated in malignant tissues vs. corresponding healthy tissues; higher in distant metastases than in the corresponding primary tumor, and higher in primary tumors that have already undergone metastatic spread or will manifest metastases, than primary tumors with no metastatic behavior. Further in support, applicants present data from their publication manuscript demonstrating the elevated 7a5/Prognostin levels in graphs A and B. Metastases have a higher 7a5/prognostin expression than primary tumors, which in turn have higher expression levels than normal tissue. The graphs use the term "MACC1 mRNA"

which is the name presently given to 7a5/prognostin. A Declaration that MACC1 is another name for 7a5/prognostin may be provided by the Applicants.

Further support that elevated levels of 7a5/prognostin may be prognostic in the case of unknown/ occult metastases, are cases where metastases are found but the origin of the primary tumor is unknown. If 7a5/prognostin were elevated in a tissue, it would be indicative of a metastatic tumor and a primary tumor at another site.

Claim 39 (new claim 46) was rejected as being indefinite for failing to point out and distinctly claim subject matter which applicant regards as the invention. The meaning of "specifically hybridizes to" was not clear. Claim 39 (46) has been amended to contain the hybridization conditions found in instant application on page 27, lines 11-13, and page 23 line 3.

Claims 10-13, 20, 39, and 41 are rejected because the Examiner finds that the specification is enabling for a method for the diagnosis of colon cancer, wherein said colon cancer is metastasizing, but does not provide enablement for a method of diagnosing other tumor disease, wherein said tumor disease is metastasizing. Applicant refers to the response above, that 7a5/prognostin is an indicator for metastases that may have a primary tumor in an unknown site.

The Examiner states that one cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not have examples or guidance for diagnosing any other cancer than colon cancer, nor is there any guidance for detecting prognostin in a biological sample of a bodily fluid. Claims 10 and 13 have been amended to remove "body fluids." The present application claims the comparison of 7a5/Prognostin between pathologic and healthy tissue samples. This comparison may be performed between samples of any tissue. Also, the overexpression of 7a5/Prognostin may be used to identify malignant tissue that has metastasized. The origin of those metastases may not necessarily be the colon, especially since tumors often de-differentiate as they progress.

With respect to diagnosing other tumor diseases, applicants have detected 7a5/prognostin in 25 primary mammary carcinoma/breast cancers and would be happy to provide the data in a declaration for the examiner. All of the breast tumors examined have been found to express 7a5/prognostin.

The Examiner states that the role of prognostin in cancer is unclear, and references Tockman *et al.* for considerations necessary for a cancer biomarker to have a successful clinical application. Applicant believes instant specification provides a conclusive link between 7a5/prognostin and metastasis. As tumors progress they revert to a less differentiated state. The tumor of origin of said metastasis may thus be any tumor that overexpresses 7a5/prognostin.

The Examiner references Slamon *et al.* that other essential factors known to be important in the prognosis of breast cancer such as size of primary tumor, stage of disease at diagnosis, hormonal receptor status and number of axillary lymph nodes involved with disease are critical to assessing relapse, survival and prognostic factors. In response, the factors of Slamon *et al.* are not applicable to colon cancer. Tumor size and regional nymph node metastasis (Wolmark *et al.*, 2006), and tumor size and metastasis and survival (Miller *et al.*, 1985) are not related in colon cancer. Also, hormone receptor status is not a factor for colon cancer as it is in breast cancer. The other essential factors of breast cancer are not applicable for colon cancer. The title page of Wolmark *et al.* and the abstract of Miller *et al.* are included for the Examiner's convenience.

In response, the Applicants have examined a series (n=25) of primary breast carcinomas, where all of the patients had not developed distant metastases at the time of analysis. Some patients have shown metachronous metastasis. The levels of 7a5/prognostin show an up to 140-fold increase in expression. The different amounts of expression are a promising basis for prognostic value in breast cancer.

The Examiner states that cancers that originate from different tissue types would present differently, and thus it would not be predictably expected that a connection between AXL, breast, and prostate cancer, and cancer invasivity,

would be established between different cancer types. The Examiner states that it is not possible to extrapolate a correlation between 7a5/prognostin in any tumor type other than colon cancer. Applicant believes that any metastatic cells capable of taking root in distant organs, such as liver or lung, must share traits that enable survival at that site. 7a5/prognostin overexpression confers an invasive ability that has more to do with acquisition of traits for metastasis such as extravasation and survival in the blood stream than the physiology of various primary tumors.

Claims 20 and 41 are rejected as failing to comply with the written description requirement. The Examiner believes the applicant claims subject matter that was not described in the specification. The specification discloses only one nucleic acid (SEQ. ID No: 1), but not derivatives of SEQ. ID No: 1, no polypeptides with homology to SEQ. ID No: 2, or polymorphisms of 7a5/Prognostin. The Examiner quotes a standard requiring "a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." The standard cites (Enzo Biochem) "that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics..." Instant application has disclosed the nucleotide and amino acid sequence (complete structure), and identified functional characteristics by highlighting various domains. Fig. 3 lists the amino acid sequence, and the location of specific motifs.

Therefore, the written description requirement is met by the listing of the amino acid sequence, identification of functional domains, the encoding nucleic acid sequence, and the derivative nucleic acid sequences which one skilled in the art would identify as encoding the nucleic acid.

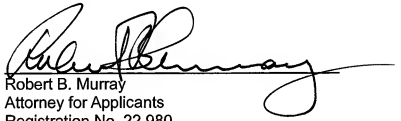
In response to the rejection of claim 20 (new claim 45), wherein the Examiner does not see a definition in the specification for "derivatives," support for "derivatives" is found on page 4, line 21 of the specification. The derivatives are described as coding for polypeptides with a specific amino acid sequence and display 80% homology at the amino acid level without the biological activity of the polypeptides being significantly reduced. Applicant believes that one skilled in the art would recognize the nucleic acid sequences that produce the identical amino acid sequences due to the codon/ anticodon wobble in the third position of a codon. The degenerate genetic code is what one skilled in the art would identify as the amino acid sequences that yield identical amino acid products using the wobble hypothesis. The use of "derivatives" in claim 20 states that the "derivatives ...are coding for the polypeptides with the amino acid sequence given in SEQ ID No: 2..." One skilled in the art would be able to identify the various nucleic acids that code for the SEQ ID No: 2 via the wobble hypothesis.

Claims 20, 39, and 41 are rejected as being anticipated by Bayer Corp. (WO 02/29086). Bayer claims a method of diagnosing colon cancer comprising determining the expression of a nucleic acid in a pathologic tissue in comparison

to healthy tissue. Claim 20, as new claim 45, is amended to "A method of determining metastatic potential." Bayer does not associate its sequence with metastasis. Bayer claims methods of "determining the phenotype of cells" but does not define "phenotype." Moreover, the gene is only functional when it is the full length gene, thus, the disclosure of portions of the gene, namely 354 base pairs of the 2559 nucleotides of the complete gene, does not anticipate the present claims.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections. Early and favorable action is awaited.

Respectfully submitted,



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Journal Article

Absence of a relationship of size of primary colon carcinoma with metastasis and survival

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Abstract This retrospective study analysed the relationship of tumor size to regional and systemic metastasis and to survival according to stage of disease. Colon cancers (391 cases) that were treated surgically at M. D. Anderson Hospital from 1955 to 1975 were reviewed. Staging of disease was based on the Astler-Coller modification of Dukes' staging classification. The mean diameters (cm±s.e.m.) of Dukes' B_1, B_2, C_2 and D tumors were 4·47±0·34 (n=46), 6·61±0·29 (n=147), 5·39±0·23 (n=71) and 5·78±0·24 (n=120), respectively. The mean diameter of Dukes' B_2 tumors was significantly greater than C_2 ($P<0·001$) and D

(P<0·05) tumors. Within stage B and C, size of the primary tumor showed no relationship to five year adjusted survival. Our findings suggest that colon carcinoma metastasis and survival are independent of tumor size. Because tumor burden does not account for distant disease, specific tumor cell phenotypes and biological processes are probably more important in determining metastatic disease.

References secured to subscribers.